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EXAMINER
GRASER, JENNIFER E

ART UNIT	PAPER NUMBER
1645	

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/555,139	Applicant(s) Agisteribbe et al.
	Examiner Jennifer Graser	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Oct 2, 2002*

2a)☒ This action is **FINAL.** 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-26* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18)☐ Interview Summary (PTO-413) Paper No(s). _____

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other:

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

The Examiner of Record has changed from Examiner Lynette Smith back to Examiner Jennifer Graser.

1. Acknowledgment and entry of the Amendment submitted 10/2/02, Paper No. 12B is made. Claims 10-26 are currently under examination.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 10-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-26 are vague and indefinite because it is unclear what is encompassed by the term "particulate immunogen". The Webster's II New Riverside University Dictionary defines the word 'particulate' as "Of, relating to, or made up of separate particles". Clarification is requested. Based on the dictionary definition, a "protein or peptide antigen" is being considered to encompass the scope of the term a 'particulate immunogen' for the purposes of this examination. This rejection from the Office Action mailed 1/10/02 was never addressed by

Applicants. The specification at page 4, lines 19-23, state that "particulate" means any association of viral, bacterial, or fungal antigens characteristic of the respective micro-organisms". It appears that peptides and proteins fit this description. Clarification is requested.

Claims 10-23 are vague and indefinite for the term "adjuvanting amount". How is this amount quantitated?

Claims 10, 16, 18, 19 and 20 are vague and indefinite due to the phrase "characteristic of *E.coli*". It is unclear whether this statement is intended to imply that the heat-labile enterotoxin is the one from *E.coli* or something else. It is suggested that the claims be amended to "from *E.coli*" in order to eliminate ambiguity. This will include the scope of the claim that Applicant desires, i.e., recombinant as well as naturally obtained, and will clear up the ambiguity associated with the phrase 'characteristic of'.

Claim 13 is vague and indefinite due to the term "derived". The term "derived" does not provide the character or properties from the source that are to be retained in the final product, e.g., paper is derived from wood but is very different from wood. The phrase "derived from" should be changed to "isolated from".

Claim 14 is vague and indefinite due to the phrase "characteristic of a micro-organism". It is unclear whether this statement is intended to imply. It is suggested that the claims be amended to "from a micro-organism" in order to eliminate ambiguity. This will not change the scope of the claim.

Claims 18 and 20 are vague and indefinite because it is unclear what is meant by a " 'common' mucosal immune response". Applicants have argued that a "common mucosal immune response" would include a mucosal response normally caused by an immunogen. They also refer to page 2, lines 15-29, of the specification. However, this passage and Example 6 do not use the term "common' mucosal immune response. Accordingly, it is unclear what is intended by the term. Applicants should amend the claim to include a more clear meaning as supported by the specification, i.e., a T-cell independent IgG and a secretory IgA local response. Appropriate correction is requested.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 10 and 12-26 remain rejected under 35 U.S.C. 102(b) as being anticipated by Tamura et al. (US 5,182,109).

Tamura et al disclose a vaccine preparation comprising in combination a vaccine and a bacterial toxin adjuvant. It is specifically disclosed that the toxin can be a B subunit of *E.coli* heat-labile enterotoxin or part of said B subunit or the B subunit of *Cholera* toxin, i.e., completely free of A subunit or toxic LT or CT holotoxin. It is further taught that the vaccine contained in the vaccine preparation can be influenza vaccine. Tamura teach that the vaccine can

be intranasal vaccine or can be in injectable form, spray form or oral administration form. Column 3, lines 12-25, specifically recite that nasal inoculation of the B subunit of Cholera toxin with the influenza HA vaccine led to a 64-fold higher level of serum HI antibodies than the HA vaccine alone. Also, intraperitoneal or subcutaneous inoculation of the B subunit of Cholera toxin with the influenza HA vaccine led to a 4-8 times higher level of serum HI antibodies than the HA vaccine alone. The paragraph concludes by stating that "[i]t has been found that CTB is an effective *adjuvant* which stimulates nasal anti-HA-IgA antibody production when administered intranasally together with HA vaccine. Further, it is disclosed that CT/LT is more effective than CTB or LTB as an adjuvant; however, CT and LT are highly toxic with known side effects. CTB alone (without CT holotoxin) and LTB alone (without LT) were still shown to be effective adjuvants and, unlike CT or LT, present no problems upon intranasal administration (see column 8, lines 56-57). The instant claims do not differ structurally from those taught by Tamura. Methods for the induction of a mucosal immune response as well as a systemic immunoglobulin response are also taught.

Response to Applicant's arguments:

Applicants argue that Tamura fail to disclose at least on particulate antigen. This has been fully and carefully considered but is not deemed persuasive. Tamura discloses the use of at least one influenza antigen. This appears to be the same antigen as is instantly claimed. Further, the term "particulate" has been defined by the specification at page 4, lines 19-23, as any

association of viral, bacterial, or fungal antigens characteristic of the respective micro-organisms. The HA influenza antigens disclosed by Tamura fall under this definition.

Applicants further argue that Tamaura does not disclose that its B subunits are free of A subunit and toxic LT holotoxin and/or toxic CT holotoxin. This has been fully and carefully considered but is not deemed persuasive. In fact, Tamura does several comparisons of the isolated CTB and the CT holotoxin. It is disclosed that CT is more effective than CTB as an adjuvant; however, it is highly toxic with known side effects. CTB alone, without CT holotoxin, is still shown to be an effective adjuvant and, unlike CT, presents no problem upon intranasal administration (see column 8, lines 56-57). The instant claims do not differ structurally from those taught by Tamura.

Applicants have stated that Tamura did not actually achieve the results they claimed to have achieved in the Patent. The Examiner cannot question the validity of a US Patent. Tamura specifically teach that CTB alone, without holotoxin, was found to be an effective adjuvant. The fact that other journal articles by the inventor Tamura mention the use of holotoxin when using recombinant LTB does not effect the instant rejection which teaches that CTB/LTB subunits effectively acted as adjuvants with HA influenza vaccine and did not require the use of holotoxin. The compositions taught in the Tamura patent do not structurally differ from the compositions recited in the instant claims. Accordingly, the compositions taught by Tamura

would inherently possess any of the properties of Applicants' claimed compositions, including the ability to provide an adjuvant effect without the use of holotoxin.

Lastly, Tamura J.Immunol, 1992, 149(3):981-988, teach the use of CTB without any trace of CT holotoxin was an effective adjuvant.

6. Claims 10-21 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Hirst et al (WO 90/06366).

Hirst et al disclose heat-labile toxin B subunit fusion proteins. The fusion proteins are prepared by recombinant DNA methodology. The LTB gene was well known. Page 5, lines 10-17, disclose a means for recombinantly producing the LTB subunit. It is disclosed that fusion proteins in which an antigen or epitope is fused to the carboxy-end of LTB represents a way of effectively presenting the antigen or epitope to the immune system. LTB is the carrier for the antigen/epitope. It is disclosed that any amino acid sequence having biological activity may be fused to the carboxy-terminus of the LTB. The antigen or epitope may be derived from a virus, bacterium, fungus, yeast or parasite. More specifically, the antigen may be derived from influenza virus, see page 3, line 23. It is also taught that attenuated live vaccines capable of expressing the fusion protein or killed toxigenic strains of E.coli in which the fusion protein has been expressed may also be used as vaccines. The vaccine may be administered orally, parenterally, or by any convenient means.

Response to Applicants' Arguments:

Applicants argue that Hirst fails to disclose at least on particulate antigen. This has been fully and carefully considered but is not deemed persuasive. Hirst specifically discloses the use of influenza antigen. This appears to be the same antigen as is instantly claimed. Additionally, Hirst recites numerous other viral, bacterial, or fungal antigens that may be used in their compositions. The term "particulate" has been defined by the specification at page 4, lines 19-23, as any association of viral, bacterial, or fungal antigens characteristic of the respective micro-organisms. The antigens disclosed by Hirst fall under this definition.

Applicants further argue that Hirst does not specifically state that is compositions are fee of holotoxin. This argument has been fully and carefully considered but is not deemed persuasive. Hirst teaches the nucleotide sequence specifically for the B subunit and teaches how to make this subunit recombinantly. This recombinant production of B subunit would not contain any other antigens, such as holotoxin, and would be highly purified. The instant claims do not differ structurally from the teachings of Hirst. Accordingly, since holotoxin is not needed in the identical compositions claimed by Applicant, it would not be needed in the compositions of Hirst either.

7. Claims 10 and 12-26 remain rejected under 35 U.S.C. 102(b) as being anticipated by Kikuta et al or Hirabayashi et al.

Kikuta and Hirabayashi both teach vaccine compositions comprising influenza HA antigens and cholera toxin subunit B. The vaccines induced both high levels of antiviral nasal IgA and serum HI antibodies, as well as complete protection against the homotypic virus

infection. The vaccine composition of either Kikuta et al or Hirabayashi et al are identical to the claimed vaccine compositions. It is specifically disclosed that the B subunit of cholera toxin (CTB) used in their experiments was purchased from Sigma Chemical and did not reveal any detectable contamination with A subunit as determined by SDS-PAGE. Additionally, pyrogen activities which could be accounted for by contaminating substances such as lipopolysaccharide were not detected in the CTB preparation. See top of page 244, column 1, from Hirabayashi and top of page 596, column 1, from Kikuta et al.

Response to Applicants' Arguments:

Applicants further argue that the references do not inherently disclose that their compositions are fee of holotoxin. This argument has been fully and carefully considered but is not deemed persuasive. Contrary to Applicants' assertion, it is specifically disclosed that the B subunit of cholera toxin (CTB) used in their experiments was purchased from Sigma Chemical and did not reveal any detectable contamination with A subunit as determined by SDS-PAGE. Additionally, pyrogen activities which could be accounted for by contaminating substances such as lipopolysaccharide were not detected in the CTB preparation. See top of page 244, column 1, from Hirabayashi and top of page 596, column 1, from Kikuta et al.

8. Claims 10-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Fujisawa et al (US 5241053).

Fujisawa et al teach fusion protein compositions produced and expressed recombinantly, comprising the gene encoding LTB and glycoprotein D from herpes simplex virus. The reference

teaches that the fusion proteins may be formulated into vaccine compositions and administered to animals (col. 1-6, 7-12, abstract and claims). The fusion protein compositions and methods of the prior art are the same as the claimed vaccine compositions and methods.

Response to Applicants' Arguments:

Applicants argue that the reference fails to disclose at least one particulate antigen. This has been fully and carefully considered but is not deemed persuasive. The reference specifically discloses the use of glycoprotein D from herpes simplex virus. The term "particulate immunogen" has been defined by the specification at page 4, lines 19-23, as any association of viral, bacterial, or fungal antigens characteristic of the respective micro-organisms. The antigen disclosed by Fujisawa appears to fall under this definition.

As was stated in the 112, second paragraph above, it is unclear what is encompassed by the term "particulate immunogen". The Webster's II New Riverside University Dictionary defines the word 'particulate' as "Of, relating to, or made up of separate particles". Clarification is requested. Based on the dictionary definition, a "protein or peptide antigen" is being considered to encompass the scope of the term a 'particulate immunogen' for the purposes of this examination. This rejection from the Office Action mailed 1/10/02 was never addressed by Applicants. The specification at page 4, lines 19-23, state that "particulate" means any association of viral, bacterial, or fungal antigens characteristic of the respective micro-organisms". It appears that peptides and proteins fit this description. Clarification is requested.

Applicants further argue that the reference does not specifically state that is compositions are fee of holotoxin. This argument has been fully and carefully considered but is not deemed persuasive. The reference teaches the nucleotide sequence specifically for the B subunit and teaches how to make this subunit recombinantly. This recombinant production of B subunit would not contain any other antigens, such as holotoxin, and would be highly purified. The instant claims do not differ structurally from the teachings of Fujisawa. There is no structural difference between the claimed compositions and those taught by Fujisawa. Accordingly, Fujisawa's compositions do not require the use of holotoxin either.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JGraser 11/14/03

Jennifer Graser
Primary Examiner
Art Unit 1645